IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: JAIN et al.

Title: CONTROLLED RELEASE NANOPARTICULATE COMPOSITIONS

Serial No.: 09/337,675

Filing Date: June 22, 1999

Examiner: A. Pulliam

Art Unit: 1615

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

The undersigned, Rajeev A. Jain, hereby declares as follows:

1. I received my Ph.D. degree in 1998 from the University of Rhode Island in Pharmaceutical Sciences. I have been working in the field of drug nanoparticle technology since February 1998, when I joined NanoSystems LLC. This business was then sold and became known as Elan Drug Delivery.

2. Currently I am a Senior Associate at Elan Drug Delivery, with offices at 3000 Horizon Drive, King of Prussia, PA 19406.

3. I am an inventor of the above-referenced application for "Controlled Release of Nanoparticulate Compositions."

4. I submit this declaration to establish that the pending claims of the present application are not obvious in view of U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge").

5. I understand that the Examiner has cited this patent against the application in Office Actions dated April 9, 2003, January 15, 2003, July 23, 2002, April 10, 2001, and August 29, 2000. In that regard, I understand the Examiner's position to be that some of the surface stabilizers taught by Liversidge can function as rate-controlling polymers, thereby allegedly rendering controlled release nanoparticulate drug compositions an obvious invention.

6. I disagree with the Examiner's position. By design, the nanoparticulate drug compositions of Liversidge allow for rapid dissolution and, therefore, rapid onset of drug action. Solid dose forms of nanoparticulate active agent dispersions disclosed by Liversidge will not exhibit controlled release of the component active agent, such that release of the active agent extends for about 2 up to about 24 hours, as required by Applicant's claims.

7. This is because solid dose controlled release compositions according to the invention require: (1) a nanoparticulate active agent in combination with a surface stabilizer, **and** (2) a rate controlling polymer present in a matrix around the nanoparticulate active agent particles or in a film coating the composition. This additional component is not taught or suggested by Liversidge. Moreover, given the rapid release of the nanoparticulate active agents of Liversidge, it was not expected that controlled release formulations of such compositions could be made. Accordingly, the development of solid dose controlled release nanoparticulate drug formulations was surprisingly unexpected.

8. In response to the Advisory Action of August 13, 2003, I present the data which exemplifies the rapid dissolution of solid dose compositions made according to Liversidge, in contrast to the controlled release compositions of the claimed invention.

9. The compositions described in the examples of Liversidge are liquid dispersions of: (1) danazol and polyvinylpyrrolidone (PVP) (Examples 1-5); (2) steroid A and lecithin (Examples 6 and 14); (3) steroid A and Triton® X-200 (an alkyl aryl polyether sulfonate) (Example 7); (4) steroid A and gum acacia (Example 8); (5) steroid A and sodium lauryl sulfate (SLS) (Example 9); (6) steroid A and docusate sodium (DOSS) (Example 10);

and (7) steroid A and Pluronic® F68 (a block copolymer of ethylene oxide and propylene oxide) (Examples 11, 12, and 14).

10. Applicants were not able to readily form dry powders or solid dosage forms of the nanoparticulate dispersion of Steroid A described in the examples of Liversidge. Drugs such as Steroid A are extremely difficult to spray dry or spray granulate, processes which are utilized in the formation of a solid dosage form, due to the risk of inhalation. Steroid A, also known as 5β,17β,-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17- ol, is a proprietary steroid developed by Sterling Drug. The U.S. Food and Drug Administration has established five categories which indicate the potential of a systemically absorbed drug for causing birth defects. Most steroids are categorized as FDA pregnancy category C. This means that in animal reproduction studies the drug has shown an adverse effect on the fetus, but there are no adequate and well-controlled studies in humans. Many steroids has shown to be teratogenic and embryocidal in the mouse and rabbit. For example, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. *See e.g.,* http://www.rxlist.com/cgi/generic/beclonas_wcp.htm (Exhibit 1). Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Moreover, some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse demonstrated fluticasone propionate to be terotogenic (cleft palate) when administered subcutaneously at doses 14 times the human topical dose. *See* http://www.rxlist.com/cgi/generic/flovent_wcp.htm (Exhibit 2).

11. The data and dissolution experiments described below reference six active agents: Danazol, Compound A (a leukotrine inhibitor), Compound B (a kinase inhibitor), Compound C (an antiviral agent), Compound D (an anticonvulsant), and naproxen. The following surface stabilizers, also taught by Liversidge, were utilized: PVP, SLS, and DOSS. In addition, dissolution results utilizing the surface stabilizers hydroxypropyl cellulose (HPC) are described.

12. The data below show that irregardless of the active agent, solid dosage forms of nanoparticulate active agents exhibit rapid release. In the absence of the additional structural element claimed by Applicants (matrix or coating), controlled release of the component active agent over a period of about 2 to about 24 hours will not be obtained.

13. Moreover, the data below also demonstrate that the presence of conventional excipients used in solid dose forms of pharmaceutical active agents does not result in controlled release of the component nanoparticulate active agent. Such excipients are frequently used, but not required, to optimize a commercial formulation.

a. Dissolution Tests for Nanoparticulate Danazol

14. The following paragraphs describe preparation and evaluation of a solid dose form of Danazol with the surface stabilizer PVP.

15. Two danazol dispersions were prepared by dissolving PVP in water, dispersing the danazol substance, and milling the aqueous danazol/PVP mixture by use of an agitating bead mill. The dispersions were milled to a final danazol mean particle size of between 150-250 nm.

16. The danazol pharmaceutical compositions were prepared by spray coating the nanoparticulate danazol dispersions onto four different solid carriers at varying levels of film dispersing agent (additive) and danazol content. The carriers were: sugar beads, granular sugar, maltodextrin, and Avicel pH 200. The table below provides a general ratio of danazol to film dispersing agent and danazol to substrate.

TABLE 1

Sample	Ratio of Film Dispersing Agent to Danazol; mg/gm	Grams Danazol/Substrate	Substrate
1	low	low	Sugar beads
2	High	High	Sugar beads
3	low	High	Sugar beads
4	High	Low	Sugar beads
5	Low	Low	maltodextrin
6	high	high	maltodextrin

TABLE 1			
Sample	**Ratio of Film Dispersing Agent to Danazol; mg/gm**	**Grams Danazol/Substrate**	**Substrate**
7	Low	High	maltodextrin
8	High	Low	maltodextrin
9	low	low	Granular sugar
10	high	high	Granular sugar
11	High	Low	Granular sugar
12	Low	High	Granular sugar
13	low	Low	Avicel
14	High	High	Avicel
15	low	High	Avicel
16	High	Low	Avicel

17. The beads were tested for aqueous dissolution rate using a distek 6 vessel dissolution bath at 37° C., stirring at 300 rpm using paddles. Test media was 1 liter distilled water, equilibrated to 37° C. A stainless steel sampling probe was connected to tygon tubing, and an Ismatec SA peristaltic pump was used to control flow at about 0.18 ml/min. An inline 0.020 μm filter was used to remove particulate danazol and carrier debris and to ensure that danazol detected was actually in solution. A fresh filter was used for each test vessel. An amount of formulation equivalent to 20 mg of danazol was added to the test vessel and absorbance was monitored continuously for 20 minutes at 285 nm using a Waters 990 Photodiode Array system. The Waters 990 software was then used to form a rate plot by taking the differential of the absorbance vs. time curve. The maximum point on the rate plot was noted as the maximum rate of aqueous dissolution. The Avicel carrier used in this study was insoluble. The Avicel PH 200 was sized at approximately 60 μm (uncoated) and retained its form as an insoluble particle during the dissolution process. Because of it's size, a 10 μm solvent filter was placed on the end of the stainless steel sampling probe preventing clogging of the probe and the 0.020 μm in-line filter.

18. Sample preparation for Aqueous Redispersion Particle Size Analysis: (A) High Danazol Content Formulations: An amount of formulation equivalent to 50 mg of danazol was weighed into a 4 ml glass vial to which 1 ml of distilled water (room temperature) was added. The vial was capped and the contents vortexed vigorously for 10 seconds. The prepared sample was then shaken at 300 rpm, 37° C. for 10 minutes using a LabLine Shaker Incubator, after which danazol particle sizing was performed. (B) Low

Danazol Content Formulations: An amount of formulation equivalent to 50 mg of danazol was weighed into a 20 ml glass scintillation vial to which 5 ml of room temperature distilled water was added. The vial was capped and the contents vortexed vigorously for 10 seconds. The prepared samples were then shaken at 300 rpm, 37° C for 10 minutes using a LabLine Shaker Incubator, after which danazol particle sizing was performed. For Avicel PH 200 samples, the Avicel PH 200 carrier was removed by filtering through a 5 μm filter just prior to sizing.

19. For sizing using the Zetasizer III, samples were diluted in filtered (0.45 μm) distilled water, and degassed before analysis. The AZ4 cell was used for all sizing procedures. Run time for size determinations was typically 120 seconds. Output from the Zetasizer III consisted of a mean particle size in nm and a 90% < value.

20. For sizing using the Coulter N4MD, samples were briefly vortexed then diluted 10 μl to about 15 ml in filtered (0.22 μm) deionized water. Diluted samples were shaken to obtain a homogeneous suspension. A 4.5 ml cuvette was cleaned and filtered (0.22 μm) deionized water, filled half way with filtered water, and sonicated for about 5 seconds to remove air bubbles. A minimal amount of the diluted sample was then added to impart a slight opaqueness to the contents of the cuvette. The cuvette was capped and inverted several times to allow proper mixing. The outside of the cuvette was siped completely dry and clean and placed into the sizing chamber which was maintained at 37° C. The viscosity setting was 0.693 cp and the refractive index was set to 1.331. The cuvette contents were adjusted as necessary to achieve a sample intensity in the range of 1.5×10^5 to 2.5×10^5 counts/second. Run time for particle sizing was typically 200 seconds. Output consisted of a mean particle size in nm, standard deviation, and a % Dust value.

21. As shown in Table 2 below, all of the solid dose nanoparticulate danazol formulations exhibited a dissolution rate far below that exhibited by Applicants' claimed compositions, *e.g.*, much less than 2 hours or greater. All of the solid dose forms showed complete dissolution in less than about 30 min. Moreover, the data in Table 2 shows that the amount of excipient does not dramatically affect the dissolution rate, as all of the formulations exhibited dissolution rates, and complete dissolution, far below that required by

Applicants' claims.

TABLE 2

Substrate	Sample	Mean Max. Aqueous Dissolution Rate (x 10^{-5} AU/min.)	Mean Time to Max. rate (Min.)	Danazol Mean Particle Size (Zetasizer III) (nm)	D90 Danazol Particle Size (Zetasizer) (nm)	Coulter N4md mean Danazol size (nm)
Sugar beads	1	5.3	3.6	299	670	371
	2	8.0	2.6	213	410	240
	3	3.1	4.4	271	580	274
	4	6.4	2.0	223	430	268
maltodextrin	5	7.0	3.0	972	2200	> 3 µm
	6	8.3	2.6	343	730	267
	7	8.0	2.3	653	1150	> 3 µm
	8	6.9	3.0	307	680	331
Granular sugar	9	7.4	2.8	241	500	262
	10	9.0	2.8	214	390	211
	11	6.0	2.8	210	380	229
	12	8.4	2.8	306	700	289
Avicel	12	5.0	3.1	250	490	278
	14	6.5	3.0	229	370	212
	15	3.2	3.2	254	525	254
	16	6.2	3.0	214	400	219

b. Dissolution Tests for Nanoparticulate Compositions of Compound A

22. The following paragraphs describe preparation and evaluation of a solid dose form of a nanoparticulate dispersion of Compound A with the surface stabilizers PVP and SLS.

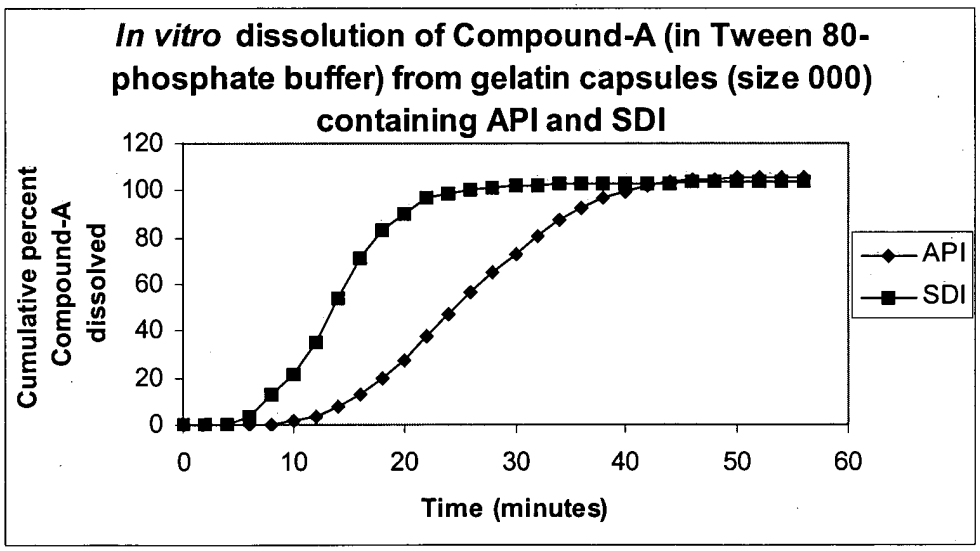
23. A nanoparticulate dispersion of Compound A was prepared by wet milling a mixture of 30% (w/w) drug, 6% (w/w) PVP, and 0.15% (w/w) SLS. The mean particle size of the milled Compound A dispersion was 118 nm, with 90% of the Compound A particles having a size of less than 196 nm ("D90"). Particle size was measured using a Horiba LA-910 Laser scattering particle size distribution analyzer.

24. This dispersion was then spray dried using a B-191 Buchi Mini Spray Dryer, with an outlet (product) temperature of 25-35° C to form a spray dried powder.

25. 225 mg of the spray dried powder of the nanoparticulate dispersion of Compound A ("SDI"), and 225 mg of unmilled Compound A ("API"), were filled in size 000 gelatin capsules and compared for drug dissolution. A Distek dissolution system (USP Method I, basket at 100 rpm) was used, with capsules of both the milled and unmilled compounds placed in glass vials. A 1% Tween® 80-phosphate buffer at 37° C and the wavelength of 260 nm were employed.

26. Figure 1 shows the results of *in vitro* dissolution studies for the nanoparticulate spray dried powder of Compound A (SDI) and the unmilled Compound A powder (API).

Figure 1



27. As shown in the above results, the solid dosage form of the nanoparticulate dispersion of Compound A (SDI) exhibited a higher dissolution rate than the unmilled drug (API). Moreover, complete dissolution of the solid dosage form of the nanoparticulate dispersion of Compound A occurred in just over 20 minutes. This time period is well below the minimum of 2 hours required by the claims of the present application.

c. Redispersibility Tests for Nanoparticulate Compositions of Compound B (kinase inhibitor)

28. The following paragraphs describe preparation and evaluation of a solid dose form of a nanoparticulate dispersion of Compound B, a kinase inhibitor, and PVP and DOSS as surface stabilizers.

29. A nanoparticulate dispersion of Compound B was prepared by wet milling a mixture of 30% (w/w) drug, 6% (w/w) PVP, and 0.3% (w/w) DOSS. The mean particle size of the milled Compound B dispersion was 142 nm, with a D90 of 197 nm. Particle size was measured using a Horiba LA-910 Laser scattering particle size distribution analyzer.

30. The nanoparticulate dispersion of Compound B was then converted to a Granulation Feed Dispersion ("GFD"), following by spray granulation over fluidized Mannitol-35 powder to form a Spray Granulated Powder. Redispersibility of the SGP was then determined.

31. The GFD of the nanoparticulate dispersion of Compound B ("NCD") was prepared by adding xylitol to the NCD. The GFD comprised 18.2% (w/w) drug, 3.63% (w/w) PVP, 0.72% (w/w) DOSS, 9.1% (w/w) xylitol, and 68.4% (w/w) water.

32. The spray granulation of the GFD of Compound B was performed using a Vector FL-Multi-1 spray granulator. The GFD was sprayed on to fluidized Mannitol-35 powder to form a spray granulated powder ("SGP"). The SGP comprised: 34.8% (w/w) drug, 7.0% (w/w) PVP, 1.4% (w/w) DOSS, 17.4% (w/w) xylitol, and 39.4% (w/w) mannitol. This process formed small granules, which uniformly contain the active and excipients. Six batches of the SGP were made.

33. The redispersibility of the six batches of SGP was evaluated in DI Water. SGP equivalent to 50 mg of drug was redispersed in 5 grams of aqueous media in separate vials. The mixture was then vortexed and incubated at 37^0C in an oven for 30 minutes. The samples were then tested for particle size using the Horiba LA 910 Laser Scattering Particle Size Distribution Analyzer.

34. Redispersibility analysis showed that 100% of the solid dose forms of the nanoparticulate Compound B redispersed in less than 45 minutes. This time period is well below the minimum of 2 hours required by the claims of the present application.

35. The redispersibility results are significant, as redispersibility is predictive of the dissolution rate of a solid dosage form. The dissolution rate of a dosage form can be expressed mathematically by the simplest form of the Noyes-Whitney equation[1(1-3)]:

$$dM/dt = [DS(C_s-C_t)]/h$$

where dM/dt is the rate of dissolution or the drug at time t, D is the diffusion coefficient of the drug in the solvent, S is the total amount of drug substance surface area present, C_s is the saturation solubility of the drug in the solvent, C_t is the concentration of drug in solvent at time t, and h is the thickness of the concentration gradient between the surface of the drug particle and the point in the bulk solvent at which the concentration of drug is equal to C_t. Thus, the dissolution rate is directly proportional to the total amount of drug substance surface area present.

36. The total amount of drug substance surface area for a given dose of drug can be described by the surface area to volume ratio:

$$4\pi r^2 / 4/3\pi r^3 = 3/r$$

Thus, for a given amount of drug substance having particles with a radius = r, the total amount of surface area is inversely proportional to the particle radius. When drug nanoparticles present in a solid dosage form are introduced into a liquid medium such as water, they may reconstitute as primary nanoparticles or as aggregates of nanoparticles. The latter are expected to have much larger effective particle sizes, and therefore smaller amounts of surface area and slower dissolution rates than the primary nanoparticles. Solid dosage forms which are fully redispersible are those which reconsitute to primary nanoparticles and retain the high amounts of surface area and rapid dissolution rates associated with

[1] Noyes, A.; Whitney, W.R., *J. Am. Chem. Soc.*, **1997**, *19*, 930-934; Hintz, R.J.; Johnson, K.C., *Int. J. Pharmaceutics*, **1989**, *51*, 9-17; Wang, J.; Flanagan, D.R. *J. Pharm. Sci.*, **1999**, *88*(7), 731-738.

nanoparticulate formulations. Since redispersibility is an indirect measure of the total amount of drug substance surface area present in a reconstituted system, it is predictive of the rate of dissolution of the drug substance in that system.

d. Redispersibility Tests for Nanoparticulate Compositions of Compound C (antiviral agent)

37. The following paragraphs describe preparation and evaluation of a solid dose form of a nanoparticulate dispersion of Compound C (an antiviral agent) and PVP as a surface stabilizer.

38. A nanoparticulate dispersion of Compound C was prepared by wet milling a mixture of 20% (w/w) drug and 4% (w/w) PVP. The mean particle size of the milled Compound C dispersion was 126 nm, with a D90 of 193 nm. Particle size was measured using a Horiba LA-910 Laser scattering particle size distribution analyzer.

39. The nanoparticulate dispersion of Compound C ("NCD") was converted to a Coating Feed Dispersion ("CFD") by the addition of DOSS and Mannitol-35. The CFD comprised: 19.01% (w/w) drug, 3.81% (w/w) PVP, 3.81% (w/w) mannitol, 1.14% (w/w) DOSS, and 72.19% (w/w) purified water.

40. The CFD was then bottom-sprayed onto 45/60 Paulaur Sugar beads using a Vector FL Multi-1 with 6" Wuster Insert to provide a solid dosage form of beads. These beads were then encapsulated using a Futura MG-2 capsule filling machine.

41. Redispersibility of the beads was evaluated in DI Water. The beads equivalents to 50 mg of drug were redispersed in 5 gram of aqueous media in separate vials. The mixture was then vortexed and incubated at 37^0C in an oven for 30 minutes. The samples were then analyzed for particle size, using the Horiba LA 910 Laser Scattering Particle Size Distribution Analyzer.

42. Redispersibility analysis showed that 100% of the solid dose forms of the nanoparticulate Compound C redispersed in less than 45 minutes. This time period is well below the minimum of 2 hours required by the claims of the present application.

e. Redispersibility Tests for Nanoparticulate Compositions of Compound D (anticonvulsant)

43. The following paragraphs describe preparation and evaluation of a solid dose form of a nanoparticulate dispersion of Compound D, an anticonvulsant, and PVP and DOSS as surface stabilizers.

44. A nanoparticulate dispersion of Compound D was prepared by wet milling a mixture of 10% (w/w) drug, 2% (w/w) PVP, and 0.1% (w/w) DOSS. The mean particle size of the milled Compound D dispersion was 134 nm, with a D90 of 180 nm. Particle size was measured using a Horiba LA-910 Laser scattering particle size distribution analyzer.

45. The nanoparticulate dispersion of Compound D ("NCD") was spray dried with and without excipients. 10 grams of the NCD were used for each batch. The resultant spray-dried powders were then evaluated for redispersibility in D.I. water. The spray drying of the nanoparticulate dispersion of Compound D with various formulations was performed using a Buchi B-191 mini spray dryer. The inlet temperature was 100°C and a flow rate at 10% on pump setting.

46. The first spray dried powder contained drug, DOSS, and PVP (a spray dried powder of the NCD). The second spray dried powder contained additional DOSS, which was added to the NCD prior to spray drying (PVP: DOSS ratio of 1:0.15 (w/w)). The third spray dried powder contained additional DOSS and mannitol, which were added to the NCD prior to spray drying (PVP: DOSS ratio of 1:0.15 (w/w), and drug : mannitol ratio of 1: 0.2 (w/w)). The fourth spray dried powder contained additional DOSS and mannitol, which were added to the NCD prior to spray drying (PVP: DOSS ratio of 1:0.15 (w/w), and drug : mannitol ratio of 1: 0.3 (w/w). A summary of the components of the four spray dried powders is shown in the table below.

Spray Dried Powder Batch Number	Components
1	82.6% (w/w) drug, 16.5% (w/w) PVP, 0.8% (w/w) DOSS
2	81.3% (w/w) drug, 16.3% (w/w) PVP, 2.4% (w/w) DOSS
3	69.9% (w/w) drug, 14.0% (w/w) PVP, 2.1% (w/w) DOSS, 14.0% (w/w) mannitol
4	65.4% (w/w) drug, 13.1% (w/w) PVP, 2.0% (w/w) DOSS, and 19.6% mannitol

47. The redispersibility of the spray dried powders was evaluated in DI Water. The spray dried powder equivalent to 50 mg drug were redispersed in 5 g of aqueous media in separate glass vials, vortexed for 10 seconds, and then incubated at 37°C in an oven for 30 minutes. The samples were then tested for particle size on the Horiba LA-910 laser scattering particle size distribution analyzer.

48. All of the solid dose forms of Compound D completely redispersed within 45 minutes or less. This time period is well below the minimum of 2 hours required by the claims of the present application.

f. Dissolution Tests for Nanoparticulate Compositions of Naproxen

49. The following paragraphs describe preparation and evaluation of a solid dose form of a nanoparticulate dispersion of naproxen and HPC as a surface stabilizer.

50. A high energy media milling process was used to make a nanoparticulate dispersion of naproxen, comprising 25% (w/w) naproxen and 2.5% HPC. A surface stabilizer solution was first prepared by dissolving 0.23 kg HPC in 6.53 kg purified water in a 20L containing using a propeller mixer. Naproxen was dispensed incrementally into the surface stabilizer solution until the entire amount was added. A media mill was charged with 0.5 mm SDy-20 polymeric media (Eastman Kodak, Rochester, NY) at a 80% load. The media mill and container were connected in a closed-loop configuration with a peristaltic pump installed at the inlet of the media mill grinding chamber to circulate the product nanosuspension at 100

mL/min. The media milling operation was complete when a mean volume of the naproxen particle size distribution of 90% < 400 nm was obtained.

51. Following the media milling operation, the resultant nanoparticulate naproxen dispersion was spray dried. The spray drier was assembled in a co-current configuration using a rotary atomization nozzle. The nanosuspension was fed to the rotary atomizer operated at 150 RPM using a peristaltic pump.

52. A dry granulation operation was used to manufacture tablets containing 200 mg naproxen and having a total average weight of 400 mg. Required amounts of naproxen/HPC spray dried powder (0.88 kg) and croscarmellose sodium (0.18 kg) were hand screened through a 60 mesh screen and blended in a 16 qt. twin shell blender for 15 minutes. The blended material was compacted using a roller compactor at 12 tons pressure and feed auger speed of 20 RPM. The compacted material was granulated using a CoMil at 925 RPM with a 0.75R screen.

53. At the completion of the granulation, lactose hydrous (0.15 kg) was screened through a 80 mesh screen and blended with the above granulation for up to 15 minutes in a 16 qt. twin shell blender. Magnesium stearate (6 g) was screened through a 80 mesh screen, added to the 16 qt. twin shell blender, and blended for up to 5 minutes.

54. The blended materials were discharged and compressed into tablets using a tablet press with caplet shaped tooling. The blended materials were loaded into the feed hopper and gravity-fed into the die cavities. The tablet press operating conditions were set to meet thickness (5.25 m), hardness (10 kp), and weight (400 mg) specifications.

55. The resulting tablets were then tested for disintegration and dissolution times. The dissolution test was conducted in 0.1M phosphate buffer at pH 6.0. The nanoparticulate naproxen tablet disintegrated in 95 seconds, and exhibited 80% dissolution in 7 minutes. This time period is well below the minimum of 2 hours required by the claims of the present application.

g. Conclusion

56. These data demonstrate the rapid disintegration and dissolution of solid dose forms of nanoparticulate active agents.

57. Given the differences in formulation and result between the nanoparticulate compositions of Liversidge and the controlled release nanoparticulate compositions of the claimed invention, the claimed invention cannot be considered obvious. The incorporation of nanoparticulate drugs into controlled release formulations was unexpected, and provided surprising results.

58. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.

Rajeev Jain

Rajeev A. Jain

23 December 03

Date